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REVIEW

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Aging-associated interleukin-11 drives the molecular mechanism and targeted therapy of idiopathic pulmonary fibrosis

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Abstract

Idiopathic pulmonary fibrosis (IPF) is an unexplained interstitial lung disease in which senescence is a central risk factor. Senescent cells drive chronic inflammation and fibrosis by the secreting senescence-associated secretory phenotype (SASP). Interleukin-11 (IL-11), a core factor in the SASP, is significantly upregulated in IPF lung tissues.IL-11 promotes lung cellular senescence and chronic inflammation through the activation of the JAK2/STAT3 and MEK/ERK1/2 pathways. It also leads to extracellular matrix protein deposition by promoting fibroblast–myofibroblast transformation, epithelial mesenchymal transition and endothelial mesenchymal transition. Targeting IL-11 has antiaging and fibrotic effects. Nanoparticle delivery therapeutic regimens targeting IL-11 show potential in animal models of IPF, but evidence for their clinical application is lacking. Future studies should focus on the dynamic molecular regulatory mechanisms of IL-11 in IPF, as well as the development of targeted delivery systems and multitarget combined intervention therapeutic regimens. This review systematically analyzes the molecular mechanisms of IL-11 in IPF and provides new perspectives for the treatment of aging-associated pulmonary fibrosis.

Keywords Idiopathic pulmonary fibrosis, Interleukin-11, Aging, Molecular mechanisms, Targeted therapy

Introduction

Idiopathic pulmonary fibrosis (IPF) is an irreversible interstitial lung disease of unknown cause [1, 2]. The main pathological features are repeated damage and repair of alveolar epithelial cells (AECs), overproduction of myofibroblasts, and excessive deposition of the extracellular matrix (ECM) [3–5]. The risk factors, such as aging, genetics, environmental exposure, and viral infections can increase the risk of developing IPF [6–9]. Aging is considered to be an independent risk factor for IPF [6, 10], which is prevalent in older adults over the age of 60 years, and the risk of developing the disease increases progressively with age [11, 12].

Lung cellular senescence arises from the induction of endogenous factors (e.g. telomere shortening, DNA damage, mitochondrial dysfunction, etc.) and exogenous factors (e.g. dust, smoking, radiation) [3, 13–15]. Senescent cells exhibit irreversible cell cycle arrest, alterations in

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cell metabolism and cell morphology and secrete a variety of cytokines, chemokines and growth factors, most notably the senescence-associated secretory phenotype (SASP) [16–18]. With increasing age, senescent cells accumulate in the body, and secreted SASP can drive cell, tissue, and organ senescence, as well as promote the emergence of fibrotic diseases [3]. Interleukin-11 (IL-11), an important factor in SASP, is correlated with longevity, has increased expression in senescent organisms, and its expression is elevated in a variety of senescence-associated diseases, such as IPF [19–23].

IL-11 is associated with several fibrotic diseases [24]. Aging, fibrosis and chronic inflammation can lead to increased levels of the IL-11 protein in human lung tissues [25]. IL-11 is derived mainly from fibroblasts and epithelial cells in IPF lung tissues; exerts prosenescence, inflammatory and fibrotic effects; and plays an important role in the progression of IPF [20, 26]. The serum IL-11 level/percent predicted forced vital capacity (%FVC) in patients was found to be an independent risk factor for predicting acute exacerbation and the prognosis of IPF [27]. Therefore, some studies have used IL-11 as a target for the treatment of IPF and have demonstrated its potential for preventing pulmonary fibrosis [26]. However, some other studies have shown that anti-IL-11 therapy does not completely block IPF progression [28]. Therefore, there is currently controversy about the central role of IL-11 in IPF.

Therefore, investigating the specific mechanisms by which IL-11 promotes the progression of IPF may provide new strategies for the intervention and treatment of IPF. In this study, we reviewed the expression of IL-11 released by senescent lung cells in IPF, the related signaling pathways and the role of IL-11 in lung cells and discussed the potential of IL-11 as a therapeutic target in IPF.

The SASP alters the microenvironment of lung cell survival and promotes cellular senescence and fibrosis (Fig. 1A)

With increasing age, the proportion of senescent cells in the lung increases, and the structure and function of senescent cells are altered. SASPs produced by senescent lung cells undergo senescence-associated chronic sterile inflammation that drives the senescence of young cells and affects the normal physiological function of the lungs [29–32].SASPs include cytokines, chemokines, growth factors, extracellular matrix proteins, and proteases [29–31]. Many senescent cells, such as type II alveolar epithelial cells (AT2s), fibroblasts, and vascular endothelial cells (VECs), have been found to be present in IPF lung tissue [3, 33–35]. These cells show shortened telomere length and abnormal chromatin remodeling during senescence, leading to the expression of high levels of senescence marker proteins, such as the cell cycle inhibitors p21, p16, p53 and senescence-associated beta-galactosidase (SA-beta-gal) [36–40]. These senescent cells secrete large amounts of SASP components involved in the formation of the chronic inflammatory microenvironment in the lung. Under the stimulation of a senescence-associated chronic inflammatory microenvironment, senescent lung cells also express programmed death ligand 1 (PD-L1), which assists senescent cells in immune escape and affects the clearance of senescent lung cells [39], opening a vicious cycle in which senescent lung cells accumulate.

Senescent lung cells have increased susceptibility to fibrosis, and some of the factors associated with the SASP, such as transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and IL-11, are profibrotic [19, 26]. They can drive senescent AECs, fibroblasts and VECs to undergo epithelial–mesenchymal transition (EMT), fibroblast–myofibroblast transition (FMT), and endothelial–mesenchymal transition (EndMT) and produce a large number of ECMs [35, 41–45], such as alpha-smooth muscle actin (α–SMA), fibronectin, and collagen type I (col I), etc. Interestingly, IL-11 is an intersection where TGF-β, PDGF, and FGF exert profibrotic effects [19]. Therefore, the study of the specific molecular mechanisms and cellular effects of IL-11 in IPF is important for the future treatment of IPF.

Molecular mechanisms of IL-11 in IPF

IL-11 is a member of the interleukin-6 (IL-6) family, and IL-11 protein expression is barely detectable in healthy individuals [26, 46, 47]. Initially, thought to be involved in immunomodulation and hematopoiesis, IL-11 was later shown to have no significant correlation with hematopoiesis [48]. IL-11 is known to be involved in development, aging, inflammation, and fibrosis and is associated with poor prognosis in a variety of diseases, such as non-small cell lung cancer [48, 49]. As the body ages, IL-11 protein expression increases, is involved in the development of aging-associated chronic sterile inflammation, and is implicated in the development of aging-associated diseases, such as IPF [20, 50].

Among the multiple profibrotic factors involved in IPF, TGF-β plays a major role. Telomere dysfunction leads to cellular senescence and concomitant activation of TGF-β1-associated pro-fibrotic signaling pathway to promote lung fibrosis progression [51], but because of the pleiotropic nature of TGF-β, the inhibition of TGF-β function results in more side effects [52–55]. Therefore, IL-11 has attracted much attention as a downstream core factor for the profibrotic effects of TGF-β [52]. In vitro studies suggest that lung fibroblasts, epithelial cells, macrophages,

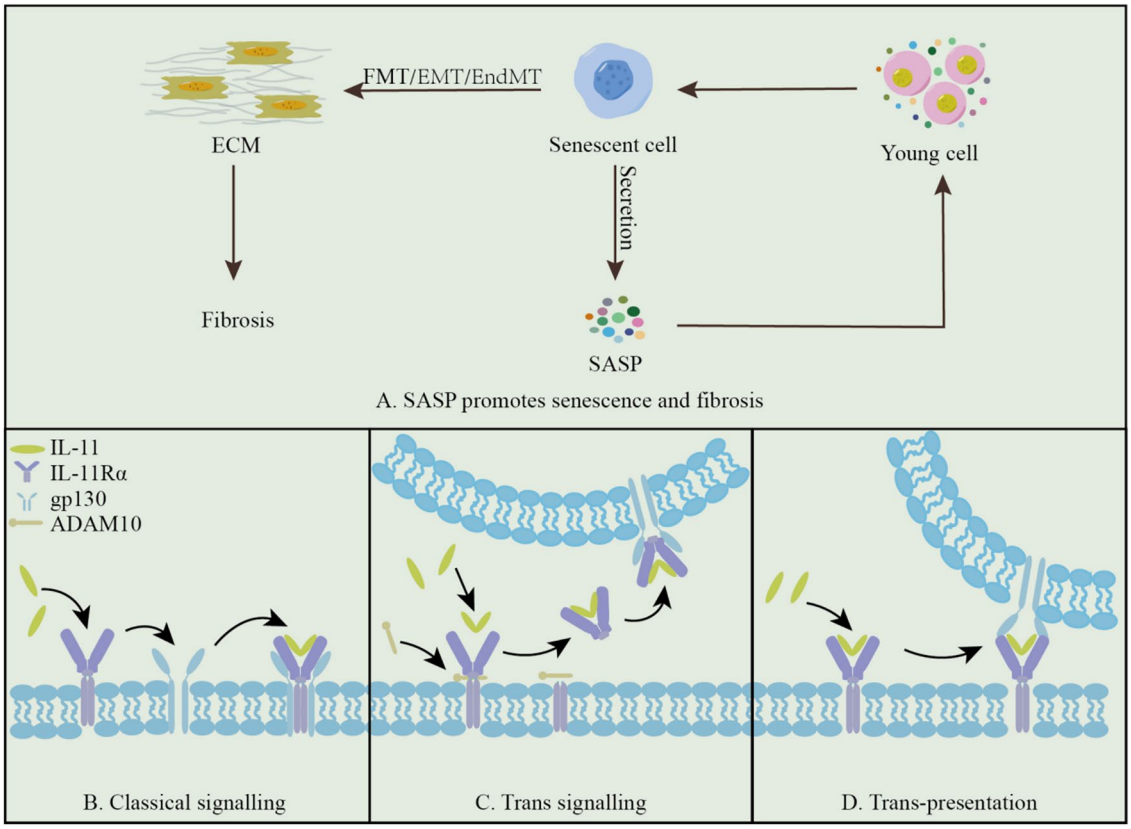

Fig. 1 A SASP promotes senescence and fibrosis: senescent cells in the lung secrete the SASP. The SASP results in a chronic inflammatory microenvironment around young cells and promotes cell senescence. Senescent cells, such as fibroblasts, alveolar epithelial cells, and vascular endothelial cells, transform into ECM-secreting stromal cells through FMT, EMT, and EndMT to induce fibrosis. B Classical signaling: IL-11 binds to IL-11Rα and gp130 on the cell membrane to activate downstream signaling pathways. C Trans-signaling: IL-11 binds to sIL-11Rα cleaved by ADAM10 and interacts with gp130 on the cell membrane to activate downstream signaling pathways. D Trans-presentation: After binding to IL-11Rα-expressing cells, IL-11 binds to another gp130-expressing cell to activate downstream signaling pathways

and airway smooth muscle cells can express IL-11, but in vivo studies related to IPF have revealed that IL-11 is derived mainly from fibroblasts and damaged epithelial cells and is expressed mainly in AT2 cells at the end stage of the disease [26, 56–61]. IL-11 is a downstream crossroads of multiple profibrotic factors and plays both proinflammatory and profibrotic roles in IPF [25, 26, 62, 63]. Therefore, IL-11 is a cytokine with the potential to be a therapeutic target for IPF. IL-11 also exerts positive feedback regulation on some profibrotic factors, such as TGF-β [64]. However, there is a lack of information on the specific mechanisms by which IL-11 plays a role in IPF, which may lead to the neglect of a potential therapeutic target.

Mode of binding of IL-11 to the receptor

IL-11 in IPF lung tissues mainly forms a hexameric complex with interleukin-11 receptor alpha (IL-11Rα) and glycoprotein 130 (gp130) on cell membranes, which then activates the downstream signaling pathway of gp130. The expression of IL-11Rα and gp130 varies in different cell membranes in the lung. Previous studies have suggested that IL-11Rα expression is increased in mesenchymal and epithelial cells, such as fibroblasts, vascular smooth muscle cells (VSMCs), VECs, and AECs, and is involved in cell proliferation and migration functions [25, 52, 61, 65–69]. However, the IL-11Rα protein was found to be expressed mainly in VSMCs and macrophages in lung tissues, as detected by immunohistochemistry in mouse lung-like organs and in precise lung sections [56], which conflicts with the results of previous studies, and future exploration of IL-11Rα protein-expressing cells in IPF lung tissues via immunohistochemistry and other methods is needed. Unlike IL-11Rα, membrane-bound gp130 is almost universally expressed in lung cells.

IL-11 binds to IL-11Rα and gp130 to form a hexameric complex, which then activates the downstream signaling pathway of gp130 [70]. This hexameric complex has also been examined in the membranes of cells that do not express the IL-11Rα receptor. Subsequently,

soluble IL-11Rα (sIL-11Rα) was found to be present in the serum [71]. On the basis of these findings, it was hypothesized that IL-11 could bind to its corresponding receptor on the cell membrane in three different ways [72]. The first is the classical signaling approach, where IL-11 binds to the transmembrane receptor IL-11Rα on the cell membrane and forms a complex with the transmembrane coreceptor gp130 (Fig. 1B) [28]. The second mode is trans signaling, where a desintegrin and metalloproteinase domain containing protein 10 (ADAM10), whose expression is elevated in IPF lung tissues, cleaves IL-11Rα from the cell surface to form sIL-11Rα. Serum IL-11 then binds to sIL-11Rα, activating the downstream pathway upon binding to gp130 on the cell membrane surface (Fig. 1C) [71, 73, 74]. The third mode of activation, trans-presentation, involves IL-11 binding to IL-11Rα on the delivering cell and binding to gp130 on the surface of neighboring cells to activate the IL-11 signaling pathway (Fig. 1D) [72, 75]. This modality may be relevant to the metastasis and adhesion of lung fibroblasts in IPF.

Relevant pathways involved in the regulation of IL-11 in IPF

IL-11 protein levels are associated with the deterioration and prognosis of IPF [20, 27, 76, 77]. IL-11 has been shown to activate the classical Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) signaling pathway and the nonclassical MRK/ERK1/2 signaling pathway in IPF [71, 78–82]. The activation of the JAK2/STAT3 signaling pathway is rapid and transient and is associated primarily with inflammation. The MRK/ERK1/2 signaling pathway is in a state of sustained activation and is associated primarily with ECM production [64]. IL-11 can also be autocratically produced by interfering with the TGF-β/Smad2/3 signaling pathway (Fig. 2). In addition, there is evidence that IL-11 is involved in the regulation of the phosphatidylinositol-3 kinase (PI3K)/AKT signaling pathway and the Notch signaling pathway in IPF [48, 56, 83, 84], but the specific mechanism has not been investigated.

JAK2/STAT3 signaling pathway

The JAK2/STAT3 signaling pathway is involved in chronic inflammation and cellular senescence in IPF

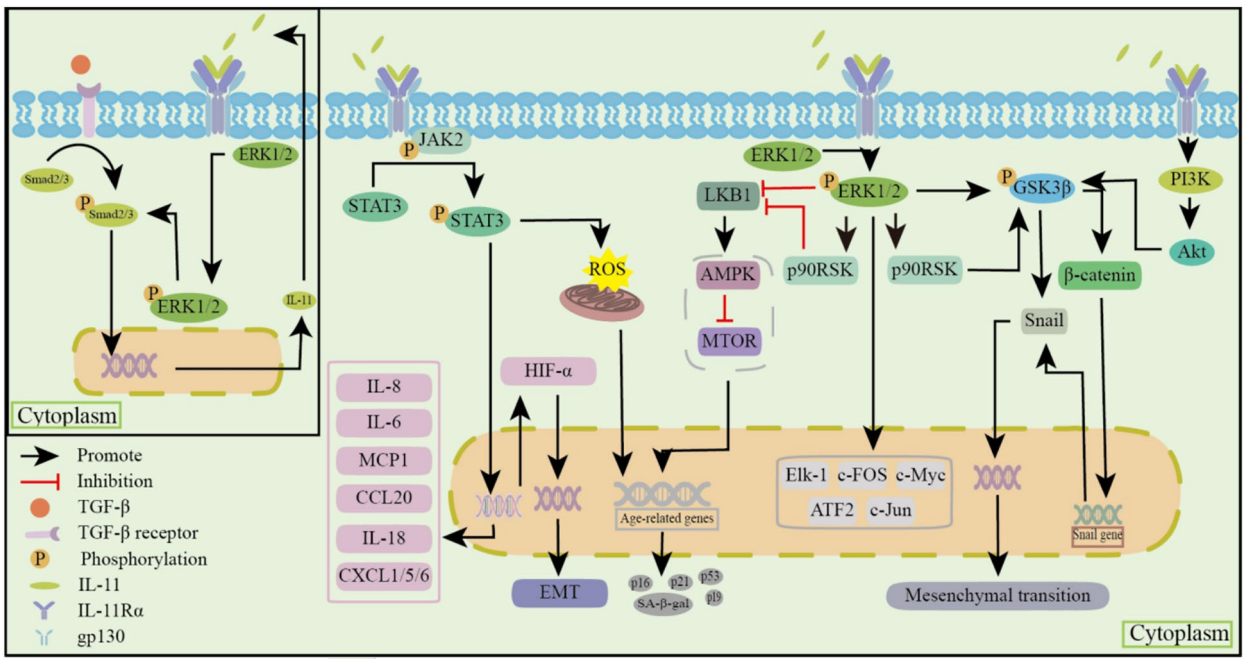

Fig. 2 Activation of the IL-11 autocrine loop: TGF-β acts on the TGF-β receptor on the cell membrane, phosphorylating Smad2/3 in the cytoplasm. p-Smad2/3 enters the nucleus to promote IL-11 gene transcription. IL-11 activated the ERM1/2 pathway downstream of gp130, and p-ERK1/2 promoted the phosphorylation of Smad2/3. IL-11 activates the JAK2/STAT3 signaling pathway: IL-11 activates gp130 to phosphorylate JAK2 on the cell membrane, and p-JAK2 aggregates and phosphorylates STAT3 in the cytoplasm. p-STAT3 can enter the nucleus and promote the entry of IL-8, IL-6, MCP1, CCL20, IL-18, CXCL1/5/6 and HIF-α. HIF-α can activate EMT-related genes. p-STAT3 can also affect the oxidative stress response in mitochondria and promote cell senescence. IL-11 activates the MEK/ERK1/2 signaling pathway: gp130 phosphorylates ERK1/2 in the cytoplasm. p-ERK1/2 promotes an increase in p90RSK, and both can inhibit LKB1 in the cytoplasm and regulate AMPK/MTOR to affect cell senescence. p-ERK1/2 and p90RSK promote GSK3β phosphorylation, resulting in increased Snail and β-catenin protein levels in the cytoplasm and promoting mesenchymal transition. IL-11 and the PI3K/AKT signaling pathway: IL-11 activates PI3K downstream of gp130, increases the Akt content, promotes GSK3β phosphorylation, and affects cell mesenchymal transition

(Fig. 2) [85, 86]. The intracellular JAK2/STAT3 signaling pathway is activated by IL-11 and phosphorylated STAT3 enters the nucleus to induce the expression of inflammatory factors. These inflammatory factors form a chronic inflammatory microenvironment and recruit immune cells to amplify the inflammatory response [84, 87–89]. In addition, p-STAT3 can promote lung fibroblast and AT2 senescence through oxidative stress [85, 90, 91]. In addition to this, it has been observed that p-STAT3 drives HIF-α transcription to promote EMT [92, 93], but the specific mechanism needs to be further explored.

MEK/ERK1/2 signaling pathway

IL-11 activates the MEK/ERK1/2 signaling pathway to promote cellular senescence and mesenchymal transition [25, 84, 94, 95]. Increased levels of IL-11 in senescent organs regulate cellular senescence through the pERK1/2-AMPK-mTORC1 axis [21, 96]. It was observed in premature and replicative cellular senescence that IL-11 could continuously phosphorylate ERK1/2 and continuously produce senescence phenotype proteins [64, 95, 97]. In addition, the senescence phenotype protein p16 also binds to p-ERK1/2, which leads to the accumulation of p-ERK1/2 in the cytoplasm [20, 98]. In addition to cellular senescence, the activated MEK/ERK1/2 signaling pathway is also involved in the regulation of intercellular mesenchymal transition and promotes ECM deposition [25, 82]. The previous studies suggested that p-ERK1/2 enters the nucleus to promote the transcription of genes related to mesenchymal transition. However, p-ERK1/2 entry into the nucleus was found to promote cellular senescence, proliferation, and differentiation gene transcription through the literature studies (Fig. 2) [99, 100]. There was no mesenchymal transition related gene transcription [101]. Therefore, the specific mechanism of IL-11/MEK/ERK1/2 signaling pathway in pulmonary fibrosis to regulate mesenchymal transition needs to be further explored. In renal tubular epithelial cells, it was found that p-ERK1/2 could promote the increase of p90 ribosomal S6 kinase (p90RSK) content in the cytoplasm and phosphorylation of glycogen synthase kinase 3-beta (GSK3β), which reduced the catabolism of Snail and β-catenin proteins in cytoplasm that promotes EMT [50, 83, 102, 103]. In fibroblasts, it has been shown that the MEK/ERK1/2 signaling pathway can promote FMT either through HIF-alpha proteins or synergistically with the TGF-β/Smad3 signaling pathway [25, 104–106]. This provides a direction for the study of the mechanism of IL-11-promoted mesenchymal transition in pulmonary fibrosis.

PI3K/AKT signaling pathway

In IPF, the PI3K/AKT signaling pathway is associated with mesenchymal transition. RNA sequencing showed that IL-11 significantly upregulated genes associated with the PI3K/AKT/MTOR pathway to drive FMT [56]. However, no involvement of IL-11/PI3K/AKT in the regulation of EMT has been identified, which is in conflict with findings in other diseases [49, 64, 107]. Therefore the specific timing of IL-11 activation of the PI3K/AKT signaling pathway to promote EMT in pulmonary fibrosis could be explored in the future.

Notch signaling pathway

The Notch signaling pathway is associated with FMT and EMT in IPF [108, 109]. There is no clear evidence that IL-11 is directly related to the Notch signaling pathway in IPF, but RNA sequencing suggests that IL-11 can affect the expression of Notch signaling pathway-related proteins [56]. In a study on cochlear hair cells, genome-wide high-throughput RNA sequencing and validation confirmed that the Notch signaling pathway is a downstream target of the MEK/ERK signaling pathway [110].

Cellular effects of IL-11 in IPF

IL-11 plays an important role in IPF by driving cellular senescence and the SASP to form a chronic inflammatory microenvironment. It also drives the transformation of lung fibroblasts, AECs, VECs and VSMCs into stromal cells via ECM secretion [20, 111].

Pulmonary fibroblasts

Lung fibroblasts can differentiate into myofibroblasts under physiological conditions to repair injury and can be rapidly eliminated after injury repair. In IPF, lung fibroblasts are the major ECM-producing cells and one of the major sources of IL-11[112]. IL-11 can promote fibroblast senescence, inflammation and FMT [20, 26, 75]. Lung fibroblasts express the senescence marker proteins p53, p16 and p21 under the induction of IL-11 [113, 114]. p16 binds to p-ERK1/2, resulting in sustained activation of the MEK/ERK pathway in myofibroblasts and the production of large amounts of ECM [20, 26]. Moreover, IL-11 induces the expression of the antiapoptotic protein Bcl-2, which leads to the accumulation of myofibroblasts in IPF lungs [115–117]. Under stimulation with IL-11, fibroblasts can promote the inflammatory infiltration of fibrotic lesions through the JAK2/STAT3 signaling pathway, inflammatory factors and chemokines [75, 118]. In mice with bleomycin-induced pulmonary fibrosis and IL-11 receptor knockout, inflammatory and fibrotic

changes in fibroblasts are significantly reduced under stimulation with IL-11 [84].

AT2s

Type I alveolar epithelial (AT1) cells, which have gas exchange functions in the physiological state, are damaged, and AT2 cells can differentiate into AT1 cells. In IPF, AT2 cells exhibit impaired differentiation capacity and undergo EMT to secrete ECM. Studies have shown that IL-11 is involved in the differentiation of AT2 cells [69, 107]. In addition, IL-11 secreted by fibroblasts can initiate EMT through cell crosstalk and affect the process of alveolar repair [56, 119]. Single-cell RNA sequencing revealed that AT2 cells expressing KRT8 specifically expressed IL-11. Moreover, IL-11 can promote the expression of KRT-8 in AT2 cells [120]. IL-11 promoted AT2 senescence through the MEK/ERK1/2 signaling pathway and increased Snail protein expression in the cytoplasm, resulting in ECM production [20, 64, 121, 122].

VECs and VSMCs

VECs and VSMCs are related to the production of ECM and complications such as pulmonary arterial hypertension (PH) in IPF. The level of IL-11 in IPF lung tissue and serum is increased, which promotes the proliferation and senescence of VECs and VSMCs and promotes pulmonary artery remodeling and pulmonary hypertension [94]. VECs and VSMCs do not express IL-11Rα, so IL-11 activates the downstream MEK/ERK1/2 signaling pathway through nonclassical signal transduction [82, 123]. Moreover, IL-11 and sIL-11Rα can increase the adhesion of myofibroblasts to the pulmonary vascular endothelial cell layer [75], which contributes to the progression of fibrosis. Cellular experiments have shown that IL-11 and soluble IL-11Rα induce the proliferation and senescence of HPAECs and HPASMCs and promote SASP expression [82]. The SASP can also stimulate hypertrophy, proliferation and migration of senescent smooth muscle cells, thereby promoting pulmonary vascular remodeling in IPF [124]. However, because the obtained IPF lung tissue samples are in the end-stage stable state, they cannot represent the whole disease process, and the interference of other diseases cannot be excluded; thus, further studies are needed for verification in the future.

The potential of targeting IL-11 for the treatment of IPF

IL-11 promotes senescence, is proinflammatory and profibrotic and plays an important role in IPF. Targeting IL-11 ameliorates inflammation, cellular senescence and ECM deposition in IPF [20, 21, 64, 125]. Pirfenidone and nintedanib improve IPF by interfering with IL-11/MEK/ERK1/2 [94]. Flufenacet attenuates IL-11-induced inflammation and fibrosis in a mouse model of bleomycin-induced pulmonary fibrosis [111]. However, the above oral drugs need to undergo gastrointestinal digestion and absorption processes, the active ingredients cannot act precisely on the lesions, and systemic toxic side effects exist. Therefore, new therapeutic options or technologies are needed for the treatment of IPF.

Inhalation therapy is uniquely suited to the treatment of lung disease because the lungs can communicate directly with the external environment through the bronchial tubes. Therefore, studies have been conducted to treat IPF by inhaling nanoparticles containing targeted IL-11, and inhalation therapy has been shown to have negligible systemic toxicity. However, the inhalation of nanoparticles containing drugs faces technical challenges, such as shear damage during nebulization, mucus permeation, cellular internalization, rapid lysosomal escape and target protein expression. Therefore, Bai, X team developed an inhalable and mucus-penetrable nanoparticle system (silL11@PPGC NPs) containing siIL-11 RNA in 2022 while achieving efficient transmucosal delivery of silL11. The nanoparticles, inhaled by noninvasive nebulization, inhibited ERK and Smad2 to suppress fibroblast differentiation and reduce ECM deposition [126]. In 2024, the team developed a new inhaled lipid nanoparticle for lung mRNA delivery, iLNP-HP08LOOP, which can promote the integration of mRNAs encoding the IL-11 single chain fragment variable (scFv) [127]. The team delivered IL-11 scFv and secreted it into the lungs of male pulmonary fibrosis model mice, significantly inhibiting fibroblast activation and extracellular matrix deposition in the lungs. A significant advantage over inhaled and intravenous IL-11 scFv [127]. In addition, Dong, ST, in 2025, developed a new inhalable small interfering RNA (siRNA) delivery system, PEI-GBZA, by piggybacking siIL-11 to target IL-11, which significantly inhibited the FMT and EMT processes, reduced neutrophil and macrophage infiltration in lesions, and alleviated fibrosis progression in an IPF model [128]. These novel targeted IL-11 treatments involving lung nebulized inhalation significantly alleviated IPF and improved lung function, but none of them showed systemic toxicity.

The studies of novel drug delivery interventions for the treatment of IPF described above illustrate the feasibility of IL-11 as a therapeutic target in animal models of IPF. However, clinical studies are lacking. Therefore, the safety and efficacy of targeted IL-11 therapy may need to be validated in future clinical studies. Moreover, the pathogenesis of IPF is not caused by a single factor, so a combination of multiple antifibrotic treatment options may be needed in the future. For example, in a study of autologous skin fibroblasts, the incorporation

of fibroblast membrane-camouflaged nanoparticles (FNPs) was effective in removing a variety of profibrotic cytokines, including TGF-β, IL-11, IL-13, and IL-17, and thus modulated the profibrotic microenvironment [129].

Future directions for IL-11 research in IPF

The research has shown that IL-11 can be used in IPF to predict acute exacerbation and the prognosis of the disease [27]. In animal and cellular experiments, IL-11 has been shown to be a promising factor in IPF with proaging, proinflammatory and profibrotic effects [20, 21]. However, the molecular mechanisms of IL-11 in IPF have not been fully explored. First, in vivo and in vitro experiments have revealed that cells expressing the IL-11 protein are different; thus, in the future, IL-11-expressing IPF cells could be probed via single-cell sequencing. The second is the signaling pathway through which IL-11 is involved in regulation. The current studies have shown that IL-11 in IPF mainly regulates the JAK2/STAT3 signaling pathway and the MEK/ERK1/2 signaling pathway. However, there is evidence that IL-11 is associated with the PI3K/AKT signaling pathway and the Notch signaling pathway [56, 83, 84], and the specific timing and conditions under which IL-11 activates these pathways need to be explored in the future.

Cellular senescence plays an important role in IPF. IL-11 promotes lung cell senescence in IPF and induces the expression of the anti-apoptotic protein Bcl-2, which inhibits senescent cell apoptosis [115]. Senolytics are a class of drugs that target senescent cells, restoring sensitivity to senescent cell apoptosis and selectively eliminating senescent cells [130]. In clinical studies of IPF, the senolytics combination of quercetin in combination with dasatinib improved the clinical symptoms of IPF [131, 132]. Thus IL-11 may be a potential target for senolytics. Therefore the specific mechanism of senolytics intervention in IL-11 pro-cellular senescence and inhibition of apoptosis in IPF can be explored in the future.

For research on IL-11 as a therapeutic target, animal and cellular experiments are mostly used at present; therefore, clinical research evidence is lacking. Therefore, the safety and efficacy of IL-11-targeted therapy can be evaluated in the future by developing organoid or humanized animal models. However, the complexity of the pathogenesis of IPF means that treatment targeting a single factor may have limited efficacy, and in the future, aerosolized inhalation multitarget therapeutic techniques may also be used to treat IPF.

The emergence of precision medicine has become a new option for the treatment of IPF patients [133, 134]. IL-11 predicts acute exacerbation and prognosis of IPF disease [27], implying that IL-11 can identify people at risk of developing IPF, predict disease progression, and also serve as a measure of treatment efficacy. Therefore, IL-11 is a potential biomarker for precision medicine treatment of IPF [134]. In the future, there is an urgent need to explore the specific IPF endotypes corresponding to IL-11 and to carry out precision-targeted therapies, which can greatly improve the effectiveness of treatment while reducing the incidence of adverse events.

Conclusion

The specific etiology of IPF is unknown, the pathogenesis is complex, and there is a lack of effective treatment options. Aging is an independent risk factor for IPF, and IL-11 can be used to predict acute exacerbation and the prognosis of IPF. IL-11 is elevated in aging organisms and exerts proaging, proinflammatory, and profibrotic effects in IPF lungs. IL-11 has antiaging and fibrotic effects, making it a promising factor for future research and treatment of IPF.

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Author contributions
JZ and QS-H designed the structure of the article; JZ and XA wrote the manuscript; XW-X, WX and DD designed and prepared the figures; QS-H and WH-L edited the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.

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